

## Durham Research Online

---

### Deposited in DRO:

18 October 2018

### Version of attached file:

Accepted Version

### Peer-review status of attached file:

Peer-reviewed

### Citation for published item:

Blecher, Ronen and Heinemann-Yerushalmi, Lia and Assaraf, Eran and Konstantin, Nitzan and Chapman, Jens R. and Cope, Timothy C. and Bewick, Guy S. and Banks, Robert W. and Zelzer, Elazar (2018) 'New functions for the proprioceptive system in skeletal biology.', *Philosophical transactions of the Royal Society B : biological sciences.*, 373 (1759). p. 20170327.

### Further information on publisher's website:

<https://doi.org/10.1098/rstb.2017.0327>

### Publisher's copyright statement:

### Additional information:

## Use policy

---

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a [link](#) is made to the metadata record in DRO
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full DRO policy](#) for further details.

## **New Functions for the Proprioceptive System in Skeletal Biology**

Ronen Blecher<sup>1,2,3\*</sup>, Lia Yarushalmi<sup>1,\*</sup>, Eran Assaraf<sup>1,2,\*</sup>, Nitzan Konstantin<sup>1</sup>, Jens R. Chapman<sup>3</sup>, Timothy C. Cope<sup>4</sup>, Guy S. Bewick<sup>5</sup>, Robert W. Banks<sup>6</sup>, Elazar Zelzer<sup>1</sup>

<sup>1</sup> Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel

<sup>2</sup> Department of Orthopedic Surgery, Assaf HaRofeh Medical Center, Zerrifin 70300, Israel, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

<sup>3</sup> Swedish Neuroscience Institute, Seattle, WA 98122 USA

<sup>4</sup> Coulter Department of Biomedical Engineering, Georgia Institute of Technology & Emory University School of Medicine, Atlanta, GA 30332 USA

<sup>5</sup> Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, Scotland, UK

<sup>6</sup> Department of Biosciences, Durham University, Durham DH1 3LE, UK

\* These authors contributed equally to this work

Corresponding author: [eli.zelzer@weizmann.ac.il](mailto:eli.zelzer@weizmann.ac.il)

## **Abstract**

Muscle spindles and Golgi tendon organs (GTOs) are two types of sensory receptors that respond to changes in length or tension of skeletal muscles. These mechanosensors have long been known to participate in both proprioception and stretch reflex. Here, we present recent findings implicating these organs in maintenance of spine alignment as well as in realignment of fractured bones. These discoveries have been made in several mouse lines lacking functional mechanosensors in part or completely. In both studies, the absence of functional spindles and GTOs produced a more severe phenotype than that of spindles alone. Interestingly, the spinal curve phenotype, which appeared during peripubertal development, bears resemblance to the human condition adolescent idiopathic scoliosis. This similarity may contribute to the study of the disease by offering both an animal model and a clue as to its etiology. Moreover, it raises the possibility that impaired proprioceptive signalling may be involved in the etiology of other conditions. Overall, these new findings expand considerably the scope of involvement of proprioception in musculoskeletal development and function.

**Keywords:** Muscle spindle, Golgi tendon organs, Adolescent idiopathic scoliosis, Proprioception, Musculoskeleton, Fracture repair

## Introduction

Proprioception, in the original Sherringtonian concept of detection of mechanical stimuli arising within the musculoskeletal system itself, is a component of the sense of the relative position of one's own body parts as well as of the level of effort exerted by acting muscles. As such, it is a necessary part of the control of movement and posture. In the musculoskeletal system of humans and other terrestrial vertebrates, the two main types of mechanosensors involved are the muscle spindle [1] and the Golgi tendon organ (GTO) [2]. By virtue of their respective positions in parallel and in series with the force-producing muscle fibres that form the great bulk of skeletal muscles, they respond predominantly to length and changing length of the muscle (muscle spindles) and to actively generated muscle force (GTOs). Although muscle spindles and GTOs are often lumped together as proprioceptors, it is important to recognize that they respond to stimuli whether arising from internal or external (e.g. gravitational) forces. Despite differences in morphology, location, measured input, effect and other characteristics [3-5], these two organs share the ability to respond to mechanical conditions in their local muscle, initiate a rapid response in specialized sensory afferent fibres, often loosely termed proprioceptive neurons, and ultimately modulate local muscle tension through segmental and longer monosynaptic and polysynaptic reflexes [6, 7]. True proprioception is typically short range, may be tonic or phasic, and is relatively weak compared to voluntary or externally evoked forces [8]. Nevertheless, here we present our recent evidence that constant disturbance in proprioception, as might occur during abnormal development or following a limb fracture, is extremely important. In order to understand some of the genetic and molecular aspects involved, we begin with a brief overview of the normal development of muscle spindles and GTOs.

Over the years, several molecular pathways have been identified to regulate proprioceptor formation, connectivity and function [9-13]. Proprioceptive neurons transmit mechanical sensations from muscles and tendons via the dorsal root ganglia (DRG) to the spinal cord. These neurons express the neurotrophic tyrosine tropomyosin receptor kinase C (*TrkC*; also known as neurotrophic tyrosine kinase receptor type 3 (*Ntrk3*) [14] along with neurogenin 2 (*Ngn2*) and Runt related transcription factor 3 (*Runx3*), all essential for the generation and development of DRG sensory neurons [15, 16]. In particular, *Runx3*, a member of the Runt domain-containing family of transcription factors, is highly expressed by DRG *TrkC*-positive neurons and is essential for their survival, axonal projection and connectivity to the spinal cord [17, 18]. *Runx3* knockout (KO) mice display severe limb ataxia, a phenotype that was recently recapitulated upon deletion of the genomic elements driving *Runx3* expression in DRG *TrkC* neurons in mice [19]. In skeletal muscles, differentiation of intrafusal (i.e., situated inside the muscle spindle) fibres begins with the establishment of neuromuscular connection between sensory afferent (Ia) neurons and primary myotubes, followed by induction from the sensory neurons. This process is regulated by neuregulin 1 (NRG1) and its receptor Erb-B2 receptor tyrosine kinase 2 (ErbB2, also known as HER2) [20]. NRG1-ErbB2 signalling activates downstream targets such as early growth response 3 (*Egr3*), a member of the zinc-finger family of transcription factors [13, 21, 22] and the Ets transcription factors Pea3 and Erm [9]. Further developed intrafusal fibres express specific intrafusal molecules, including the *TrkC* ligand neurotrophin 3 (NT3) [23] and Ets transcription factor Er81 [9]. These molecules, along with *Egr3*, Pea3 and Erm, were shown to affect the survival of proprioceptive sensory neurons and maintain functional sensory axon-myotube connection during embryonic and early postnatal muscle spindle development [9, 13].

Most of the research of the proprioceptive system has focused on its well-known function in motor control. Yet, accumulated evidence shows that this system is also involved in nonautonomous regulation of skeletal development and function. In this review, we describe recent findings pertaining to the roles of proprioception in the maintenance of proper spinal alignment, as well as in morphological restoration of fractured bones.

### **The involvement of the proprioceptive system in maintaining spinal alignment**

The vertebral column serves as the central axis of the body, playing essential roles in supporting weight and maintaining posture while allowing movement. As other skeletal elements, the spine is subjected to high stresses created by body weight and by loads exerted by the attached muscles. The unique structure of the spine restricts movement between its parts to provide inherent stability and, thereby, reduces the need for continuous external stabilization by contraction of adjacent muscles [24]. The dynamic maintenance of body posture requires tight regulation of the position and orientation of numerous vertebrae and intervertebral discs. Yet, despite its importance, surprisingly little is known about this regulatory mechanism.

Scoliosis is a condition in which the spinal column is curved laterally by 10° or more [25]. The most common type of the disease is adolescent idiopathic scoliosis (AIS), which appears during puberty without a known cause or other skeletal anomalies in around 3% of school-aged children worldwide. Treatment includes back bracing, with aim to stop the progression of deformity. In severe or rapidly progressing curves, surgical correction may be required [26]. To date, despite substantial efforts to decipher the pathogenesis of acquired scoliosis, the mechanisms underlying this condition are still elusive [27].

Because the onset of AIS is not preceded by other skeletal abnormalities, uncovering the mechanisms underlying its pathogenesis has been particularly challenging. Yet, the appearance of a curve in spines comprising morphologically intact elements suggests the involvement of a nonautonomous regulatory mechanism in maintaining spinal alignment. Indeed, we recently reported that *Runx3* knockout mice, which lack TrkC neurons connecting between proprioceptors and spinal cord, developed peripubertal scoliosis without prior vertebral dysplasia or muscle asymmetry [28]. Similar results were obtained by conditional deletion of *Runx3* in peripheral nervous tissue or specifically in peripheral sensory neurons, but not in skeletal tissue. Moreover, deletion of enhancer elements driving *Runx3* expression in proprioceptive neurons induced a similar phenotype. A less severe phenotype was exhibited by *Egr3* knockout mice, which lack muscle spindles but not Golgi tendon organs. Functional assays revealed a decrease in gait regularity, which was also more pronounced in *Runx3* KO than in *Egr3* KO mice. These findings implicate impaired proprioceptive signalling in acquired scoliosis and suggest that both receptor types are required for this regulatory mechanism.

Over the years, numerous attempts to develop genetic [29, 30], neuroendocrine [31, 32] or surgical perturbation [33, 34] models for AIS have come short of producing a model that recapitulates the unique features of the disease [27]. Our mouse model displays several hallmark features of AIS, including apparently intact skeletons prior to the appearance of scoliosis, the temporal dynamics of the deformative process, and an accentuated right-sided curve of the thoracic spine.

A large body of evidence supports the idea of neuromuscular involvement in the etiology of scoliosis. These include abnormal morphology and function of neuromuscular elements identified in the central nervous system [35, 36], the somatosensory [37] and vestibular [38] systems and in trunk muscles [39, 40] of AIS patients. Moreover, the association between neural insults, such as

stroke [41] and cerebral palsy [42], and the development of trunk imbalance and deformity is well-established in the clinical practice. In addition, both stroke [43, 44] and cerebral palsy [45] have been shown to substantially impair proprioceptive functions, suggesting a mechanistic cause for the acquired deformity. In animal models, removal of the spinal cord [46] or nerve roots [47-49] resulted in scoliosis, demonstrating the cross-species conservation of the association.

There are several observations that support the notion that proprioceptive function is impaired in AIS patients. These include reported alterations in postural balance [50, 51], and gait [52], as well as reduced number of muscle spindles in paravertebral muscles [53]. Additionally, abnormal neural proprioception-related responses, such as inability to reproduce joint angle [54], vibratory sensation [55] and the size-weight illusion, integrating proprioception and visual inputs [56] have also been seen in these patients. Also, the onset time of AIS during the second decade of life is consistent with the maturation of the proprioceptive system (refs 111, 112). Indeed, it has been speculated that proprioception is involved in the control of spine stability, with muscle spindles acting as a regulatory feedback mechanism [57, 58]; yet, direct evidence for this involvement has been lacking.

Our work may provide the missing link between proprioception and scoliosis. Our findings indicate that the proprioceptive system may not only provide dynamic control of spine alignment, but also prevents progressive spinal deformation. Moreover, our data indicate that this unique relationship between proprioception and spinal alignment requires the synergistic action of both muscle spindles and GTOs. The clinical implication of this notion is that treatment should aim at restoring the balance between motor output and sensory feedback.

In our study, the appearance of spinal deformity (between mouse postnatal days 40 and 60) coincided with highly relevant anatomical and physiological changes, namely maturation of



muscle mechanosensors [59, 60] and substantial increases in muscle mass [61] and mobility. Thus, peripubertal scoliosis could result from the combination of increasing mechanical loads and a malfunctioning proprioceptive system. Interestingly, our proprioceptive-deficient mouse strains also developed ataxia, which is not seen in AIS patients. Given the close functional and anatomical interactions between central and peripheral proprioceptive circuits, it is yet to be determined whether ataxia could contribute to the scoliotic phenotype.

From a genetic perspective, while our findings underscore the involvement of *Runx3* and *Egr3* in the mechanisms underlying AIS, the etiopathogenesis of this disease has long been considered polygenic in nature [62, 63]. To date, various loci has been identified as been associated with susceptibility to AIS [64-68]. Based on the etiological explanation we propose, the search for the genetic background of AIS should focus on genes, loci and pathways associated with proprioception. This proposed etiology may also promote development of evaluation and screening tests based on, for example, the performance of proprioception-dependent tasks. Altogether, the shift in focus in the research of AIS towards viewing it as a neuromuscular disease may lead to advances in diagnostics, in progression assessment and, possibly, to future treatment.

### **Proprioception and morphological repair of fractured bones**

Correct bone morphology is essential for the function of the musculoskeletal system [69-73]. The evidence-based textbook model for bone fracture repair describes four distinct stages, from hematoma formation through to bone modelling [74-82]. Yet, despite extensive clinical research into the association between fracture realignment and functional outcome [83-85], little attention has been paid to the mechanisms that restore the general shape of the fractured bone immediately after the injury and before union has been achieved. It is reasonable to assume that the ability to

restore skeletal morphology after a traumatic insult to bone integrity would have granted vertebrates a considerable evolutionary advantage. Indeed, several pieces of evidence support the existence of a robust mechanism that rapidly restores bone morphology following injury. In human neonates, humeral birth fractures with severe angulations usually heal well without intervention and with little residual deformity [86]. Additionally, studies of primate skeletons have documented high rates (up to 30%) of well-healed fractures, mostly occurring in youth, which were also marked by minimal residual deformity, further indicating that effective morphological restoration occurs spontaneously and frequently [87-90]. These findings suggest that during evolution, vertebrates have acquired a mechanism that realigns fractured bones [91].

Previously, we demonstrated the existence of such a mechanism by showing that fractured humeri of neonatal mice undergo realignment without any intervention [92]. The realignment process, which we dubbed natural reduction, involved substantial movement of the two fracture fragments. However, we did not identify the mechanism that senses the location and orientation of the fracture fragments to guide realignment. More recently, we found that muscle spindles and GTOs play this role together [93]. We showed that natural reduction failed in fractured bones of *Runx3*-KO mice. Conditional deletion of *Runx3* in peripheral nervous system, but not in limb mesenchyme, recapitulated the null phenotype, as did inactivation of muscles flanking the fracture site. *Egr3* KO mice displayed a less severe phenotype, suggesting that both receptor types, as well as muscle contraction, are required for this regulatory mechanism.

Bones have long been known to possess autonomous mechanosensing capabilities [71-73, 91, 94]. To cope with a dynamic mechanical environment, bones adapt their morphology [95, 96], mineral composition and density [97, 98] in response to changes in mechanical loading. At the cell level, chondrocytes [99, 100], osteoblasts [101] and osteocytes [102] have all been reported to be

mechanosensitive. Fracture callus also has mechanosensing capabilities, as has been shown both clinically [103] and experimentally [104, 105]. The finding of a proprioception-mediated mechanism that monitors and restores bone integrity adds a nonautonomous level of regulation to the current view of mechanosensing in fracture repair.

Interactions among different tissues regulate the development and growth of the musculoskeletal system [106-109]. For example, skeletal muscles have been shown to regulate the commitment of joint lineage cells [107] as well as the circumferential shape and mineral distribution of developing long bones [95]. In the same vein, it was recently suggested that muscle-derived satellite cells actively participate in fracture repair by expressing various growth factors [110]. The findings that proprioceptive circuitry and muscle activity regulate fracture repair further demonstrates the importance of such interactions between musculoskeletal tissues.

Interestingly, we showed that natural reduction becomes more effective with age. While this finding is at odds with the common knowledge on repair processes, it is consistent with the maturation of the proprioceptive system. In mice, the sensory endings of muscle spindles continue to develop until 30-40 days postnatally [59, 60]. In humans, the ability to perform proprioception-specific tasks was shown to increase from childhood into adolescence [111, 112]. These findings support the notion that proprioceptive efficiency improves with increased age, which would explain our observation.

The research of fracture repair has largely ignored the role of muscle pull in restoring bone alignment. Based on our findings, we suggest that muscle proprioceptors detect the position of the fracture fragments and guide natural reduction. According to this revised model, the breakage of the bone causes changes in length and tonus of attached muscles. Consequently, asymmetric muscle activation controlled by proprioceptive signals correct the position of misaligned fracture

fragments rapidly and effectively by pulling more strongly on the parts that are farther away from their proper location. The activation of this mechanism immediately after the injury may optimize the healing process and its outcome substantially.

### **Proprioception in aging**

Increased longevity in developed countries has long been considered an indication of great scientific and medical advancements. Nonetheless, it also poses considerable clinical and socioeconomic challenges, including a steep rise in healthcare expenditure. With advancing age, the musculoskeletal system undergoes several gradual changes leading to decline in function. For example, sarcopenia is defined as the loss of muscle mass that occurs with aging, a process that includes reduction in the muscle cross-sectional area as well as a morphologic change, ultimately resulting in a 60% reduction in muscle power [113]. A concurrent reduction in bone mineral content, known as osteopenia or osteoporosis, further exposes the aging skeleton to low-energy fragility fractures. Finally, accelerated denervation of motor neurons [114] may also contribute to increased fragility in advanced age. Similarly, various elements of the proprioceptive system also change during aging. Muscle spindles in aged animals, for example, have been shown to possess fewer intrafusal fibres [115] as well as an altered morphology of their sensory endings [116]. In addition, electrophysiological studies showed that mature muscle spindles are altered, displaying a much lower dynamic response of primary endings compared to those of young animals [116]. Taken together, both primary alteration in neural and muscular elements of the musculoskeleton and proprioception-specific changes result in a gradual decline in proprioceptive function in elderly individuals.

One of the more substantial results of this decline is general fragility, manifested in an increased tendency to fall and sustain injuries, most notably hip fractures. By providing a better sense of position, proprioception training was shown to be highly useful in the prevention of falls [117] as well as in the rehabilitation of injured patients [118].

To summarize, similar to other elements of the neuromuscular axis, the proprioceptive system undergoes significant changes with advancing age, contributing to the increased risk to sustain a fragility fracture. Better understanding of proprioceptive pathways may assist in developing specific treatments directed at halting their functional decline, or regaining it during a rehabilitation process, thereby greatly improving the well-being of the mature population.

### **The regulatory role of the proprioceptive system in musculoskeletal system: future directions**

Proprioceptive mechanosensors provide constant regulation of skeletal muscle length and tension to coordinate motor control [119]. Our recent studies implicate the proprioceptive system in regulation of both maintenance and repair of the skeleton. This increases substantially the scope of known physiological functions of this system. Moreover, this raises the possibility that the proprioceptive system is involved in regulating other processes and that its dysfunction may contribute to the etiology of various musculoskeletal pathologies.

The regulatory role of the proprioceptive system can be either nonautonomous or mediated by autonomous mechanisms. Our two recent reports provide examples for nonautonomous regulation, where the proprioceptive system serves as the sensor that activates muscles to achieve skeletal integrity and alignment. Given that the skeleton is a mechanosensitive tissue, it is tempting to speculate that the proprioceptive system can also influence the autonomous response of the skeleton to a changing mechanical environment. By modulating muscle tonus and activity, the

proprioceptive system can control the load exerted on bones, joints, tendons and ligaments. These loads can then be translated into molecular signals by mechanosensors installed within these tissues, thereby regulating both growth and steady state. The existence of such an axis implies that abnormal proprioceptive function could lead to musculoskeletal pathology.

Conceptually, there is a fundamental difference between these two modes of involvement. In mediated regulation, mechanosensors in the affected tissue convert the mechanical loads into biological input. By contrast, during nonautonomous regulation the mechanosensors within the muscle need to identify deviation in organization or morphology of skeletal tissue. The ability of the muscle via its intrinsic sensory organs to detect morphological abnormality in neighbouring tissues implies that this regulatory mechanism contains a "setpoint" from which deviations are identified and that also signals the termination of the correction process.

One mechanism that may contribute to the setpoint is the fusimotor system. The motor innervation of intrafusal fibres by gamma neurons, which innervate the polar regions of these fibres and regulate their contractile states, allows the central nervous system to control muscle spindle responsiveness to a given length or length change. In particular, increased static gamma activity produces increased tonic firing in spindle afferents. Better understanding of the fusimotor system may resolve any potential involvement in determining the aforementioned setpoint. The mechanical properties of the different intrafusal fibres are also relevant here. There are three types of intrafusal fibres, namely bag1, bag2 and chain fibres. Most muscle spindles contain one bag1, one bag2 and several chain fibres, and the action of static gamma neurons on the responsiveness of spindle afferents is due to their innervation of the bag2 and chain fibres. Better understanding of their mechanical properties and the molecular mechanism that control them may reveal important insight into the activity of the spindle.

Finally, we know relatively little on the molecular mechanisms that regulate the development, structure and activity of proprioceptive sensory organs. Their involvement in so many important functions should encourage efforts to uncover these mechanisms in order to better understand how the proprioceptive system regulates processes such as skeletal maintenance, repair and function.

**Competing interests**

We have no competing interests.

**Funding**

This review was supported by grants from the Israel Science Foundation (ISF) MORASHA Biomedical Research Program in Neurodegenerative Diseases, Genetic Disorders and Metabolic Diseases (#2147/17) and from the Estate of Bernard Bishin for the WIS-Clalit Program (to E.Z.).

## References

1. Bewick G.S., Banks R.W. 2015 Mechanotransduction in the muscle spindle. *Pflugers Arch* **467**(1), 175-190. (doi:10.1007/s00424-014-1536-9).
2. Jami L. 1992 Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. *Physiological reviews* **72**(3), 623-666. (doi:10.1152/physrev.1992.72.3.623).
3. Granit R. 1975 The functional role of the muscle spindles--facts and hypotheses. *Brain* **98**(4), 531-556.
4. Maier A. 1997 Development and regeneration of muscle spindles in mammals and birds. *Int J Dev Biol* **41**(1), 1-17.
5. Moore J.C. 1984 The Golgi tendon organ: a review and update. *Am J Occup Ther* **38**(4), 227-236.
6. Chen H.H., Hippenmeyer S., Arber S., Frank E. 2003 Development of the monosynaptic stretch reflex circuit. *Curr Opin Neurobiol* **13**(1), 96-102. (doi:10.1016/S0959-4388(03)00006-0).
7. Proske U., Gandevia S.C. 2012 The proprioceptive senses: their roles in signalling body shape, body position and movement, and muscle force. *Physiological reviews* **92**(4), 1651-1697. (doi:10.1152/physrev.00048.2011).
8. Everts E. 1981 Role of motor cortex in voluntary movements in primates. In *American Physiological Society Handbook of Physiology: Nervous System Section 1* (ed. Brooks V.), pp. 1083-1120. Bethesda, MD, Lippincott Williams and Wilkins.
9. Arber S., Ladle D.R., Lin J.H., Frank E., Jessell T.M. 2000 ETS gene *Er81* controls the formation of functional connections between group Ia sensory afferents and motor neurons. *Cell* **101**(5), 485-498. (doi:10.1016/S0092-8674(00)80859-4).
10. Cheret C., Willem M., Fricker F.R., Wende H., Wulf-Goldenberg A., Tahirovic S., Nave K.A., Saftig P., Haass C., Garratt A.N., et al. 2013 *Bace1* and *Neuregulin-1* cooperate to control formation and maintenance of muscle spindles. *Embo J* **32**(14), 2015-2028. (doi:10.1038/emboj.2013.146).
11. Friese A., Kaltschmidt J.A., Ladle D.R., Sigrist M., Jessell T.M., Arber S. 2009 Gamma and alpha motor neurons distinguished by expression of transcription factor *Err3*. *Proc Natl Acad Sci U S A* **106**(32), 13588-13593. (doi:10.1073/pnas.0906809106).
12. Hippenmeyer S., Shneider N.A., Birchmeier C., Burden S.J., Jessell T.M., Arber S. 2002 A role for *neuregulin1* signalling in muscle spindle differentiation. *Neuron* **36**(6), 1035-1049. (doi:10.1016/S0896-6273(02)01101-7).
13. Tourtellotte W.G., Keller-Peck C., Milbrandt J., Kucera J. 2001 The transcription factor *Egr3* modulates sensory axon-myotube interactions during muscle spindle morphogenesis. *Developmental biology* **232**(2), 388-399. (doi:10.1006/dbio.2001.0202).
14. Marmigere F., Ernfors P. 2007 Specification and connectivity of neuronal subtypes in the sensory lineage. *Nat Rev Neurosci* **8**(2), 114-127.
15. Ma Q., Fode C., Guillemot F., Anderson D.J. 1999 *Neurogenin1* and *neurogenin2* control two distinct waves of neurogenesis in developing dorsal root ganglia. *Genes & development* **13**(13), 1717-1728.
16. Smeyne R.J., Klein R., Schnapp A., Long L.K., Bryant S., Lewin A., Lira S.A., Barbacid M. 1994 Severe sensory and sympathetic neuropathies in mice carrying a disrupted *Trk/NGF* receptor gene. *Nature* **368**(6468), 246-249.
17. Inoue K., Ozaki S., Ito K., Iseda T., Kawaguchi S., Ogawa M., Bae S.C., Yamashita N., Itohara S., Kudo N., et al. 2003 *Runx3* is essential for the target-specific axon pathfinding of *trkc*-expressing dorsal root ganglion neurons. *Blood cells, molecules & diseases* **30**(2), 157-160.
18. Levanon D., Bettoun D., Harris-Cerruti C., Woolf E., Negreanu V., Eilam R., Bernstein Y., Goldenberg D., Xiao C., Fliegauf M., et al. 2002 The *Runx3* transcription factor regulates development and survival of *TrkC* dorsal root ganglia neurons. *Embo J* **21**(13), 3454-3463.



19. Appel E., Weissmann S., Salzberg Y., Orlovsky K., Negreanu V., Tsoory M., Raanan C., Feldmesser E., Bernstein Y., Wolstein O., et al. 2016 An ensemble of regulatory elements controls Runx3 spatiotemporal expression in subsets of dorsal root ganglia proprioceptive neurons. *Genes & development* **30**(23), 2607-2622. (doi:10.1101/gad.291484.116).
20. Leu M., Bellmunt E., Schwander M., Farinas I., Brenner H.R., Muller U. 2003 Erbb2 regulates neuromuscular synapse formation and is essential for muscle spindle development. *Development (Cambridge, England)* **130**(11), 2291-2301.
21. Oliveira Fernandes M., Tourtellotte W.G. 2015 Egr3-dependent muscle spindle stretch receptor intrafusal muscle fiber differentiation and fusimotor innervation homeostasis. *J Neurosci* **35**(14), 5566-5578. (doi:10.1523/JNEUROSCI.0241-15.2015).
22. Tourtellotte W.G., Milbrandt J. 1998 Sensory ataxia and muscle spindle agenesis in mice lacking the transcription factor Egr3. *Nature genetics* **20**(1), 87-91. (doi:10.1038/1757).
23. Ernfors P., Lee K.F., Kucera J., Jaenisch R. 1994 Lack of neurotrophin-3 leads to deficiencies in the peripheral nervous system and loss of limb proprioceptive afferents. *Cell* **77**(4), 503-512.
24. Rawls A. F.R. 2010 Development and functional anatomy of the spine. In *The genetics and development of Scoliosis* (ed. Kusumi K., Dunwoodie, Sally L), Springer.
25. SRS. 2016 Adolescent Idiopathic Scoliosis. (Scoliosis Research Society).
26. William C. Warner J.R.W.a.D.M.K. 2013 Scoliosis and Kyphosis. In *Campbell's Operative Orthopedics* (ed. S. Terry Canale J.H.B.), pp. 1703-1896, 12 ed. Philadelphia, Elsevier.
27. Ouellet J., Odent T. 2013 Animal models for scoliosis research: state of the art, current concepts and future perspective applications. *Eur Spine J* **22 Suppl 2**, S81-95. (doi:10.1007/s00586-012-2396-7).
28. Blecher R., Krief S., Galili T., Biton I.E., Stern T., Assaraf E., Levanon D., Appel E., Anekstein Y., Agar G., et al. 2017 The Proprioceptive System Masterminds Spinal Alignment: Insight into the Mechanism of Scoliosis. *Developmental cell* **42**(4), 388-399 e383. (doi:10.1016/j.devcel.2017.07.022).
29. Adham I.M., Gille M., Gamel A.J., Reis A., Dressel R., Steding G., Brand-Saberi B., Engel W. 2005 The scoliosis (sco) mouse: a new allele of Pax1. *Cytogenet Genome Res* **111**(1), 16-26.
30. Blanco G., Coulton G.R., Biggin A., Grainge C., Moss J., Barrett M., Berquin A., Marechal G., Skynner M., van Mier P., et al. 2001 The kyphoscoliosis (ky) mouse is deficient in hypertrophic responses and is caused by a mutation in a novel muscle-specific protein. *Human molecular genetics* **10**(1), 9-16.
31. Machida M., Dubousset J., Imamura Y., Iwaya T., Yamada T., Kimura J. 1995 Role of melatonin deficiency in the development of scoliosis in pinealectomised chickens. *J Bone Joint Surg Br* **77**(1), 134-138.
32. Thillard M.J. 1959 [Vertebral column deformities following epiphysectomy in the chick]. *Comptes rendus hebdomadaires des seances de l'Academie des sciences* **248**(8), 1238-1240.
33. Pal G.P., Bhatt R.H., Patel V.S. 1991 Mechanism of production of experimental scoliosis in rabbits. *Spine* **16**(2), 137-142.
34. Robin G.C. 1996 Scoliosis induced by rib resection in chickens. *Journal of spinal disorders* **9**(4), 351.
35. Shi L., Wang D., Hui S.C., Tong M.C., Cheng J.C., Chu W.C. 2013 Volumetric changes in cerebellar regions in adolescent idiopathic scoliosis compared with healthy controls. *Spine J* **13**(12), 1904-1911. (doi:10.1016/j.spinee.2013.06.045).
36. Wang D., Shi L., Chu W.C., Burwell R.G., Cheng J.C., Ahuja A.T. 2012 Abnormal cerebral cortical thinning pattern in adolescent girls with idiopathic scoliosis. *Neuroimage* **59**(2), 935-942. (doi:10.1016/j.neuroimage.2011.07.097).
37. Guo X., Chau W.W., Hui-Chan C.W., Cheung C.S., Tsang W.W., Cheng J.C. 2006 Balance control in adolescents with idiopathic scoliosis and disturbed somatosensory function. *Spine* **31**(14), E437-440.
38. Shi L., Wang D., Chu W.C., Burwell G.R., Wong T.T., Heng P.A., Cheng J.C. 2011 Automatic MRI segmentation and morphoanatomy analysis of the vestibular system in adolescent idiopathic scoliosis. *Neuroimage* **54 Suppl 1**, S180-188. (doi:10.1016/j.neuroimage.2010.04.002).

39. Acaroglu E., Akel I., Alanay A., Yazici M., Marcucio R. 2009 Comparison of the melatonin and calmodulin in paravertebral muscle and platelets of patients with or without adolescent idiopathic scoliosis. *Spine* **34**(18), E659-663.
40. McIntire K.L., Asher M.A., Burton D.C., Liu W. 2007 Trunk rotational strength asymmetry in adolescents with idiopathic scoliosis: an observational study. *Scoliosis* **2**, 9.
41. Gillen G. 2015 Trunk Control: Supporting Functional Independence. In *Stroke Rehabilitation A Function-Based Approach* (ed. G G.), 4th ed. St. Louis, Elsevier.
42. SRS. 2016 Neuromuscular Scoliosis. (
43. Dukelow S.P., Herter T.M., Moore K.D., Demers M.J., Glasgow J.I., Bagg S.D., Norman K.E., Scott S.H. 2010 Quantitative assessment of limb position sense following stroke. *Neurorehabilitation and neural repair* **24**(2), 178-187. (doi:10.1177/1545968309345267).
44. Smith D.L., Akhtar A.J., Garraway W.M. 1983 Proprioception and spatial neglect after stroke. *Age and ageing* **12**(1), 63-69. (doi:10.1093/ageing/12.1.63).
45. Smorenburg A.R., Ledebt A., Deconinck F.J., Savelsbergh G.J. 2012 Deficits in upper limb position sense of children with Spastic Hemiparetic Cerebral Palsy are distance-dependent. *Research in developmental disabilities* **33**(3), 971-981. (doi:10.1016/j.ridd.2012.01.006).
46. Barrios C., Tunon M.T., De Salis J.A., Beguiristain J.L., Canadell J. 1987 Scoliosis induced by medullary damage: an experimental study in rabbits. *Spine* **12**(5), 433-439.
47. Liszka O. 1961 Spinal cord mechanisms leading to scoliosis in animal experiments. *Acta medica Polona* **2**, 45-63.
48. MacEwen G.D. 1973 Experimental scoliosis. *Clinical orthopaedics and related research* (93), 69-74.
49. Pincott J.R., Davies J.S., Taffs L.F. 1984 Scoliosis caused by section of dorsal spinal nerve roots. *J Bone Joint Surg Br* **66**(1), 27-29.
50. Gruber A.H., Busa M.A., Gorton Iii G.E., Van Emmerik R.E., Masso P.D., Hamill J. 2011 Time-to-contact and multiscale entropy identify differences in postural control in adolescent idiopathic scoliosis. *Gait Posture* **34**(1), 13-18. (doi:10.1016/j.gaitpost.2011.02.015).
51. Lao M.L., Chow D.H., Guo X., Cheng J.C., Holmes A.D. 2008 Impaired dynamic balance control in adolescents with idiopathic scoliosis and abnormal somatosensory evoked potentials. *Journal of pediatric orthopedics* **28**(8), 846-849. (doi:10.1097/BPO.0b013e318181e1bc9).
52. Yang J.H., Suh S.W., Sung P.S., Park W.H. 2013 Asymmetrical gait in adolescents with idiopathic scoliosis. *Eur Spine J* **22**(11), 2407-2413. (doi:10.1007/s00586-013-2845-y).
53. Ford D.M., Bagnall K.M., Clements C.A., McFadden K.D. 1988 Muscle spindles in the paraspinal musculature of patients with adolescent idiopathic scoliosis. *Spine* **13**(5), 461-465.
54. Barrack R.L., Whitecloud T.S., 3rd, Burke S.W., Cook S.D., Harding A.F. 1984 Proprioception in idiopathic scoliosis. *Spine* **9**(7), 681-685. (doi:10.1097/00007632-198410000-00005).
55. Wyatt M.P., Barrack R.L., Mubarak S.J., Whitecloud T.S., Burke S.W. 1986 Vibratory response in idiopathic scoliosis. *J Bone Joint Surg Br* **68**(5), 714-718. (doi:10.1302/0301-620X.68B5.3782230).
56. Yekutieli M., Robin G.C., Yarom R. 1981 Proprioceptive function in children with adolescent idiopathic scoliosis. *Spine* **6**(6), 560-566. (doi:10.1097/00007632-198111000-00006).
57. Reeves N.P., Narendra K.S., Cholewicki J. 2007 Spine stability: the six blind men and the elephant. *Clinical biomechanics (Bristol, Avon)* **22**(3), 266-274.
58. Bergmark A. 1989 Stability of the lumbar spine. A study in mechanical engineering. *Acta orthopaedica Scandinavica* **230**, 1-54.
59. Maeda N., Osawa K., Masuda T., Hakeda Y., Kumegawa M. 1985 Postnatal development of the anulospiral endings of Ia fibres in muscle spindles of mice. *Acta Anat (Basel)* **124**(1-2), 42-46. (doi:10.1159/000146093).

60. Osawa K., Maeda N., Sato M., Kawasaki T., Masuda T., Yamamoto Y., Hakeda Y., Ukai M., Watanabe Y., Suwa T., et al. 1988 Postnatal development of the annulospiral endings of Ia fibres in muscle spindles of the mouse temporal muscle. *Anat Anz* **167**(4), 253-257.
61. Griffin G.E., Goldspink G. 1973 The increase in skeletal muscle mass in male and female mice. *The Anatomical record* **177**(3), 465-469. (doi:10.1002/ar.1091770311).
62. Ikegawa S. 2016 Genomic study of adolescent idiopathic scoliosis in Japan. *Scoliosis and spinal disorders* **11**, 5. (doi:10.1186/s13013-016-0067-x).
63. Ward K., Ogilvie J., Argyle V., Nelson L., Meade M., Braun J., Chettier R. 2010 Polygenic inheritance of adolescent idiopathic scoliosis: a study of extended families in Utah. *American journal of medical genetics* **152A**(5), 1178-1188. (doi:10.1002/ajmg.a.33145).
64. Hayes M., Gao X., Yu L.X., Paria N., Henkelman R.M., Wise C.A., Ciruna B. 2014 ptk7 mutant zebrafish models of congenital and idiopathic scoliosis implicate dysregulated Wnt signalling in disease. *Nature communications* **5**, 4777. (doi:10.1038/ncomms5777).
65. Kou I., Takahashi Y., Johnson T.A., Takahashi A., Guo L., Dai J., Qiu X., Sharma S., Takimoto A., Ogura Y., et al. 2013 Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis. *Nature genetics* **45**(6), 676-679. (doi:10.1038/ng.2639).
66. Ogura Y., Kou I., Miura S., Takahashi A., Xu L., Takeda K., Takahashi Y., Kono K., Kawakami N., Uno K., et al. 2015 A Functional SNP in BNC2 Is Associated with Adolescent Idiopathic Scoliosis. *Am J Hum Genet* **97**(2), 337-342. (doi:10.1016/j.ajhg.2015.06.01).
67. Sharma S., Londono D., Eckalbar W.L., Gao X., Zhang D., Mauldin K., Kou I., Takahashi A., Matsumoto M., Kamiya N., et al. 2015 A PAX1 enhancer locus is associated with susceptibility to idiopathic scoliosis in females. *Nature communications* **6**, 6452. (doi:10.1038/ncomms7452).
68. Takahashi Y., Kou I., Takahashi A., Johnson T.A., Kono K., Kawakami N., Uno K., Ito M., Minami S., Yanagida H., et al. 2011 A genome-wide association study identifies common variants near LBX1 associated with adolescent idiopathic scoliosis. *Nature genetics* **43**(12), 1237-1240. (doi:10.1038/ng.974).
69. Kettelkamp D.B., Hillberry B.M., Murrish D.E., Heck D.A. 1988 Degenerative arthritis of the knee secondary to fracture malunion. *Clinical orthopaedics and related research* (234), 159-169. (doi:10.1097/00003086-198809000-00029).
70. Ring D. 2005 Treatment of the neglected distal radius fracture. *Clinical orthopaedics and related research* (431), 85-92. (doi:10.1097/01.blo.0000152442.66083.ff).
71. Currey J.D. 2003 The many adaptations of bone. *J Biomech* **36**(10), 1487-1495. (doi:10.1016/S0021-9290(03)00124-6).
72. Frost H.M. 2001 From Wolff's law to the Utah paradigm: insights about bone physiology and its clinical applications. *Anat Rec* **262**(4), 398-419. (doi:10.1002/ar.1049).
73. Weiner S. W.H.D. 1998 THE MATERIAL BONE: Structure-Mechanical Function Relations. *Ann Rev Math Sci* **28**, 271-298. (doi:10.1146/annurev.matsci.28.1.271).
74. Ai-Aql Z.S., Alagl A.S., Graves D.T., Gerstenfeld L.C., Einhorn T.A. 2008 Molecular mechanisms controlling bone formation during fracture healing and distraction osteogenesis. *Journal of dental research* **87**(2), 107-118. (doi:10.1177/154405910808700215).
75. Bolander M.E. 1992 Regulation of fracture repair by growth factors. *Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine (New York, NY)* **200**(2), 165-170. (doi:10.3181/00379727-200-43410A).
76. Brighton C. 1984 Principals of fracture healing: Part I. The biology of fracture repair. In *Instructional Course Lectures XXXIII* (ed. JA M.), pp. 60-82. Saint Louis, MO, CV Mosby.
77. Cho T.J., Gerstenfeld L.C., Einhorn T.A. 2002 Differential temporal expression of members of the transforming growth factor beta superfamily during murine fracture healing. *J Bone Miner Res* **17**(3), 513-520. (doi:10.1359/jbmr.2002.17.3.513).

78. Einhorn T.A. 1998 The cell and molecular biology of fracture healing. *Clinical orthopaedics and related research* (355 Suppl), S7-21. (doi:10.1097/00003086-199810001-00003).
79. Gerstenfeld L.C., Cullinane D.M., Barnes G.L., Graves D.T., Einhorn T.A. 2003 Fracture healing as a post-natal developmental process: molecular, spatial, and temporal aspects of its regulation. *Journal of cellular biochemistry* **88**(5), 873-884. (doi:10.1002/jcb.10435).
80. Schindeler A., McDonald M.M., Bokko P., Little D.G. 2008 Bone remodeling during fracture repair: The cellular picture. *Seminars in cell & developmental biology* **19**(5), 459-466. (doi:10.1016/j.semcdb.2008.07.004).
81. Shapiro F. 2008 Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. *European cells & materials* **15**, 53-76. (doi:10.22203/eCM.v015a05).
82. Wilkins K.E. 2005 Principles of fracture remodeling in children. *Injury* **36 Suppl 1**, A3-11. (doi:10.1016/j.injury.2004.12.007).
83. Ellsasser J.C., Moyer C.F., Lesker P.A., Simmons D.J. 1975 Improved healing of experimental long bone fractures in rabbits by delayed internal fixation. *The Journal of trauma* **15**(10), 869-876.
84. Fogel G.R., Morrey B.F. 1987 Delayed open reduction and fixation of ankle fractures. *Clinical orthopaedics and related research* (215), 187-195. (doi:10.1097/00003086-199702000-00027).
85. Lam S.J. 1964 The Place of Delayed Internal Fixation in the Treatment of Fractures of the Long Bones. *The Journal of bone and joint surgery* **46**, 393-397. (doi:10.1302/0301-620X.46B3.393).
86. Husain S.N., King E.C., Young J.L., Sarwark J.F. 2008 Remodeling of birth fractures of the humeral diaphysis. *J Pediatr Orthop* **28**(1), 10-13. (doi:10.1097/BPO.0b013e3181558c67).
87. Bramblett C.A. 1967 Pathology in the Darajani baboon. *American journal of physical anthropology* **26**(3), 331-340. (doi:10.1002/ajpa.1330260308).
88. Duckworth W.L. 1911 On the Natural Repair of Fractures, as seen in the Skeletons of Anthropoid Apes. *Journal of anatomy and physiology* **46**(Pt 1), 81-85.
89. Schultz A.H. 1939 *Notes on Diseases and Healed Fractures of Wild Apes: And Their Bearing on the Antiquity of Pathological Conditions in Man*. Baltimore, Johns Hopkins University Press.
90. Schultz A.H. 1944 Age changes and variability in gibbons. A Morphological study on a population sample of a man-like ape. *Am J Phys Anthropol* **2**, 1-129. (doi:10.1002/ajpa.1330020102).
91. Currey J.D. 2002 *Bones; Structure and mechanics*, Princeton University Press.
92. Rot C., Stern T., Blecher R., Friesem B., Zelzer E. 2014 A mechanical Jack-like Mechanism drives spontaneous fracture healing in neonatal mice. *Dev Cell* **31**(2), 159-170.
93. Blecher R., Krief S., Galili T., Assaraf E., Stern T., Anekstein Y., Agar G., Zelzer E. 2017 The Proprioceptive System Regulates Morphologic Restoration of Fractured Bones. *Cell reports* **20**(8), 1775-1783. (doi:10.1016/j.devcel.2017.07.022).
94. David B Burr M.R.A. 2014 *Basic and applied bone biology*, Elsevier.
95. Sharir A., Stern T., Rot C., Shahar R., Zelzer E. 2011 Muscle force regulates bone shaping for optimal load-bearing capacity during embryogenesis. *Development* **138**(15), 3247-3259. (doi:10.1242/dev.063768).
96. Robling A.G., Castillo A.B., Turner C.H. 2006 Biomechanical and molecular regulation of bone remodeling. *Annu Rev Biomed Eng* **8**, 455-498. (doi:DOI: 10.1146/annurev.bioeng.8.061505.095721).
97. Bach-Gansmo F.L., Wittig N.K., Bruel A., Thomsen J.S., Birkedal H. 2016 Immobilization and long-term recovery results in large changes in bone structure and strength but no corresponding alterations of osteocyte lacunar properties. *Bone* **91**, 139-147. (doi:10.1016/j.bone.2016.07.005).
98. Ellman R., Spatz J., Cloutier A., Palme R., Christiansen B.A., Bouxsein M.L. 2013 Partial reductions in mechanical loading yield proportional changes in bone density, bone architecture, and muscle mass. *J Bone Miner Res* **28**(4), 875-885. (doi:10.1002/jbmr.1814).
99. Lee H.S., Millward-Sadler S.J., Wright M.O., Nuki G., Salter D.M. 2000 Integrin and mechanosensitive ion channel-dependent tyrosine phosphorylation of focal adhesion proteins and beta-

- catenin in human articular chondrocytes after mechanical stimulation. *J Bone Miner Res* **15**(8), 1501-1509. (doi:10.1359/jbmr.2000.15.8.1501).
100. Wann A.K., Zuo N., Haycraft C.J., Jensen C.G., Poole C.A., McGlashan S.R., Knight M.M. 2012 Primary cilia mediate mechanotransduction through control of ATP-induced  $\text{Ca}^{2+}$  signalling in compressed chondrocytes. *Faseb J* **26**(4), 1663-1671. (doi:10.1096/fj.11-193649).
  101. Davidson R.M., Tatakis D.W., Auerbach A.L. 1990 Multiple forms of mechanosensitive ion channels in osteoblast-like cells. *Pflugers Arch* **416**(6), 646-651. (doi:10.1007/BF00370609).
  102. Huiskes R., Ruimerman R., van Lenthe G.H., Janssen J.D. 2000 Effects of mechanical forces on maintenance and adaptation of form in trabecular bone. *Nature* **405**(6787), 704-706. (doi:10.1038/35015116).
  103. Aro H.T., Chao E.Y. 1993 Bone-healing patterns affected by loading, fracture fragment stability, fracture type, and fracture site compression. *Clinical orthopaedics and related research* (293), 8-17. (doi:10.1097/00003086-199308000-00003).
  104. Probst A., Spiegel H.U. 1997 Cellular mechanisms of bone repair. *J Invest Surg* **10**(3), 77-86.
  105. Thompson Z., Miclau T., Hu D., Helms J.A. 2002 A model for intramembranous ossification during fracture healing. *J Orthop Res* **20**(5), 1091-1098.
  106. Blitz E., Viukov S., Sharir A., Schwartz Y., Galloway J.L., Pryce B.A., Johnson R.L., Tabin C.J., Schweitzer R., Zelzer E. 2009 Bone ridge patterning during musculoskeletal assembly is mediated through SCX regulation of Bmp4 at the tendon-skeleton junction. *Dev Cell* **17**(6), 861-873. (doi:10.1016/j.devcel.2009.10.010).
  107. Kahn J., Shwartz Y., Blitz E., Krief S., Sharir A., Breitel D.A., Rattenbach R., Relaix F., Maire P., Rountree R.B., et al. 2009 Muscle contraction is necessary to maintain joint progenitor cell fate. *Dev Cell* **16**(5), 734-743. (doi:10.1016/j.devcel.2009.04.013.).
  108. Shwartz Y., Farkas Z., Stern T., Aszodi A., Zelzer E. 2012 Muscle contraction controls skeletal morphogenesis through regulation of chondrocyte convergent extension. *Dev Biol* **370**(1), 154-163. (doi:10.1016/j.ydbio.2012.07.026).
  109. Zelzer E., Blitz E., Killian M.L., Thomopoulos S. 2014 Tendon-to-bone attachment: from development to maturity. *Birth Defects Res C Embryo Today* **102**(1), 101-112. (doi:10.1002/bdrc.21056).
  110. Abou-Khalil R., Yang F., Lieu S., Julien A., Perry J., Pereira C., Relaix F., Miclau T., Marcucio R., Colnot C. 2015 Role of muscle stem cells during skeletal regeneration. *Stem Cells* **33**(5), 1501-1511. (doi:10.1002/stem.1945).
  111. Goble D.J., Lewis C.A., Hurvitz E.A., Brown S.H. 2005 Development of upper limb proprioceptive accuracy in children and adolescents. *Hum Mov Sci* **24**(2), 155-170. (doi:10.1016/j.humov.2005.05.004).
  112. Pickett K., Konczak J. 2009 Measuring kinaesthetic sensitivity in typically developing children. *Dev Med Child Neurol* **51**(9), 711-716. (doi:10.1111/j.1469-8749.2008.03229.x).
  113. Thom J.M., Morse C.I., Birch K.M., Narici M.V. 2007 Influence of muscle architecture on the torque and power-velocity characteristics of young and elderly men. *European journal of applied physiology* **100**(5), 613-619. (doi:10.1007/s00421-007-0481-0).
  114. Guillet C., Auguste P., Mayo W., Kreher P., Gascan H. 1999 Ciliary neurotrophic factor is a regulator of muscular strength in aging. *J Neurosci* **19**(4), 1257-1262. (doi:10.1523/JNEUROSCI.19-04-01257.1999 ).
  115. Swash M., Fox K.P. 1972 The effect of age on human skeletal muscle. Studies of the morphology and innervation of muscle spindles. *Journal of the neurological sciences* **16**(4), 417-432. (doi:10.1016/0022-510X(72)90048-2).
  116. Kim G.H., Suzuki S., Kanda K. 2007 Age-related physiological and morphological changes of muscle spindles in rats. *The Journal of physiology* **582**(Pt 2), 525-538. (doi:10.1113/jphysiol.2007.130120).
  117. Riva D., Bianchi R., Rocca F., Mamo C. 2016 Proprioceptive Training and Injury Prevention in a Professional Men's Basketball Team: A Six-Year Prospective Study. *Journal of strength and conditioning research* **30**(2), 461-475. (doi:10.1519/JSC.0000000000001097).

118. Lephart S.M., Pincivero D.M., Giraldo J.L., Fu F.H. 1997 The role of proprioception in the management and rehabilitation of athletic injuries. *The American journal of sports medicine* **25**(1), 130-137. (doi:10.1177/036354659702500126).
119. Windhorst U. 2007 Muscle proprioceptive feedback and spinal networks. *Brain Res Bull* **73**(4-6), 155-202. (doi:10.1016/j.brainresbull.2007.03.010).